Hepato-Cardio-Renal Syndrome

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Hepatorenal syndrome has conventionally been regarded as a multisystem syndrome in which pathophysiologic pathways that link cirrhosis with impairment in kidney function are followed by dysfunction of several organs such as the heart. The advances in cardiac studies have helped diagnose more subtle cardiac abnormalities that would have otherwise remained unnoticed in a significant subset of patients with advanced liver disease and cirrhosis. Accumulating data suggests that in many instances, the cardiac dysfunction precedes and predicts development of kidney disease in such patients. These observations point to the heart as a key player in hepatorenal syndrome and challenge the notion that the cardiac abnormalities are either the consequence of aberrancies in hepatorenal interactions or have only minor effects. As such, the disturbances traditionally bundled within hepatorenal syndrome may indeed represent a hepatic form of cardiorenal syndrome whereby the liver affects the kidney in part through cardiorenal pathways (that is, hepato-cardio-renal syndrome).

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Key Words: Cardiorenal syndrome, Heart failure, Hepatorenal syndrome, Cirrhotic cardiomyopathy

BACKGROUND

Hepatorenal syndrome (HRS) has conventionally been defined as a form of functional volume-refractory kidney failure in patients with cirrhosis and ascites. While the precise pathophysiologic mechanisms underlying HRS are not well understood, exaggerated splanchnic vasodilation with maladaptive hyperactivity of the neurohormonal axis (including sympathetic nervous system activation, nonosmotic release of arginine vasopressin, and renin-angiotensin-aldosterone system [RAAS] activation) is known to play a central role.[1] Interestingly, these neurohormonal pathways contribute to impaired kidney function in patients with heart failure as well (that is, cardiorenal syndrome). While HRS was originally thought to be primarily limited to the liver and kidneys, it has been shown to represent a syndrome of multiorgan dysfunction that includes a variety of systemic changes such as endothelial and circulatory dysfunction.[2] Emerging data obtained from more sophisticated imaging studies point to involvement of the heart in various stages of liver disease, and a specific form of cardiac dysfunction has been recognized in these patients (that is, cirrhotic cardiomyopathy).[3] As such, the role of cardiac and circulatory dysfunction in the pathophysiology of HRS has recently been the focus of much investigation, and some authors have suggested that HRS might indeed represent a form of overlap syndrome where the pathophysiologic mechanisms linking the liver and the kidney might be intertwined with those connecting cardiac dysfunction to cirrhosis and/or impairment of kidney function.[4,5] In this pathophysiologic model, the role of the heart has been brought to the forefront of the pathways linking the three organs together (that is, hepato-cardio-renal syndrome).

CIRCULATORY DYSFUNCTION IN CIRRHOSIS

Patients with cirrhosis display clinical signs such as bounding pulse, palmar erythema, and low blood pressure secondary to systemic vasodilatation, in particular in the splanchnic beds.[6] Peripheral and splanchnic vasodilatation is believed to be the primary cause of a hyperdynamic circulation and contributes to portal hypertension in patients with advanced cirrhosis.[6,7] Initially, the reduction in systemic vascular resistance can be compensated by an increase in cardiac output that maintains the effective arterial blood volume within a normal range. As liver disease and cirrhosis advance, the significant reduction in systemic vascular resistance exhausts the cardiac reserve, resulting in progressive underfilling of the arterial circulation, central hypovolemia, and low blood pressure. At this stage, there is progressive activation of neurohormonal systems such as the RAAS, sympathetic nervous system, and nonosmotic release of arginine vasopressin in an effort to restore and maintain the effective arterial blood volume and arterial pressure.[8] Similar to cardiorenal syndrome, the maladaptive activation of this neurohormonal axis, together with its resulting impairment of kidney blood flow, decreases glomerular filtration rate, reduces urinary sodium excretion, and increases water retention, which further promotes ascites formation and hyponatremia in parallel with progression of the liver disease.[9]

Circulatory changes that are an inherent consequence of cirrhosis and portal hypertension may also affect the pulmonary circulation. These changes are responsible for the development of pulmonary vascular disorders, of which hepatopulmonary syndrome is the most common (detected in 10-30% of patients evaluated for a liver transplantation).[10] The disease is characterized by intrapulmonary vascular dilatations and right-to-left shunts, resulting in impaired gas exchange, worsening quality of life, and an increase in mortality. The only definitive therapy for

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patients with hepatopulmonary syndrome is liver transplantation.

ENDOTHELIAL DYSFUNCTION IN CIRRHOSIS

While the precise mechanisms leading to systemic vasodilatation in advanced cirrhosis remain elusive, several humoral substances have been identified as potential mediators that may contribute to peripheral vasodilatation and portal hypertension (eg, adrenomedullin and endothelin).[11] Nitric oxide has been recognized as the most important vasodilator molecule in the splanchnic and systemic circulation of patients with cirrhosis.[12] Nitric oxide distribution is considered distinctive in the splanchnic circulation of patients with cirrhosis in that it is reduced in the intrahepatic microcirculation (where there is a predominance of vasoconstrictors such as angiotensin II) while it is overproduced in the remaining part of the splanchnic circulation. The net result is a progressive increase in intrahepatic vascular resistance in parallel with continuous splanchnic vasodilatation, resulting in portal hypertension.[12,13] The altered intestinal mucosal permeability and the emergence of portosystemic collaterals in advanced cirrhosis allow the exposure to a large amount of endotoxins, resulting in nitric oxide production and its downstream effects.[14]

CLINICAL SUMMARY

- Advances in cardiac studies have revealed presence of subtle cardiac abnormalities in patients with advanced liver disease and cirrhosis.
- Emerging data point to cardiac involvement as a key component in the pathophysiology of kidney dysfunction in hepatorenal syndrome.
- Current strategies for management of hepatorenal syndrome may portend their salutary impact through improvement in cardiorenal interactions (hepato-cardiorenal syndrome).
- Recognition of the significant role of cardiac dysfunction in the setting of hepatorenal syndrome may have significant diagnostic and therapeutic implications.

CIRRHOTIC CARDIOMYOPATHY

Cirrhotic cardiomyopathy is characterized by systolic dysfunction as evidenced by a blunted increase in stress cardiac output, with a resting left ventricular ejection fraction of less than 55%, impaired diastolic relaxation, prolonged isovolumetric relaxation time, and a number of electrophysiological disturbances (eg, prolonged QTC interval) in the absence of a known cardiac disease.[2] While its diagnostic criteria have been subject to discussion and evolution,[15] it has been reported to be present in up to half of patients with cirrhosis.[16] A more recent study using the new criteria for cirrhotic cardiomyopathy reported its prevalence at 55.7%.[17]

Diastolic dysfunction is considered an early and frequent marker of cirrhotic cardiomyopathy.[18] Defects in the passive tension of myofilament proteins as well as impaired myocardial relaxation (possibly related to abnormalities in calcium exchange through the sarcoplasmic reticulum) have been implicated in its pathogenesis. The diastolic dysfunction leads to an increase in the blood volume in the left atrium, which, in turn, results in an increase in the trans-mitral pressure gradient. Diastolic dysfunction can be either diagnosed noninvasively by cardiac echography or through detection of high pressures on cardiac catheterization (left ventricular end-diastolic pressure >16 mmHg or pulmonary capillary wedge pressure >12 mmHg).

Systolic dysfunction is often latent in patients with cirrhosis. Left ventricular systolic function at rest is often evaluated as normal.[19,20] Subtle abnormalities may only be detected under conditions of stress or by using newer diagnostic techniques.[21] The blunted responsiveness of the cardiac output to changes in response to volume, postural challenge, exercise, and pharmacological stress may indicate systolic dysfunction in cirrhosis. For example, after changing their posture to standing, patients with cirrhosis might paradoxically experience a decrease in the left ventricular end-systolic volume, systemic vascular resistance, and cardiac index despite a marked increase in heart rate and the activity of neurohormonal system.[22] Similarly, a number of studies have revealed a blunted cardiac response to vasoactive drugs. In a study by Epstein and colleagues, the infusion of angiotensin II produced a normalization of the systemic vascular resistance and an increase in pulmonary arterial wedge pressure (PAWP), albeit without the expected increase in cardiac output.[23] New echocardiographic techniques may be needed to identify patients with subclinical ventricular dysfunction. Two-dimensional speckle-tracking echocardiography is an imaging technique that allows the assessment of left ventricular regional myocardium and global strain in three orthogonal directions by tracking natural acoustic markers (speckles) on a frame-to-frame basis within the cardiac cycle.[24]

In a longitudinal study on cirrhotic patients with refractory ascites, baseline markers of cardiac function (eg, cardiac output and stroke volume) were found to be significantly lower in those patients who subsequently developed HRS and further decreased at the time of HRS diagnosis.[25] Of note, systemic vascular resistance remained unchanged between baseline and follow-up in these patients. The neurohormonal activity was also found to be higher in those patients whose cirrhosis progressed to HRS, which, in the face of unchanged systemic vascular resistance but disturbed cardiac output, points to the heart as the main driving factor.[25] Point-of-care ultrasound can be helpful in objective assessment of volume status as well as hemodynamics in patients with cirrhosis, with potential implications in diagnosis and management (Figure 1). Whether cardiac biomarkers such as b-type natriuretic peptide would prove helpful in early detection of patients with subtle cardiac abnormalities needs to be explored in prospective trials.

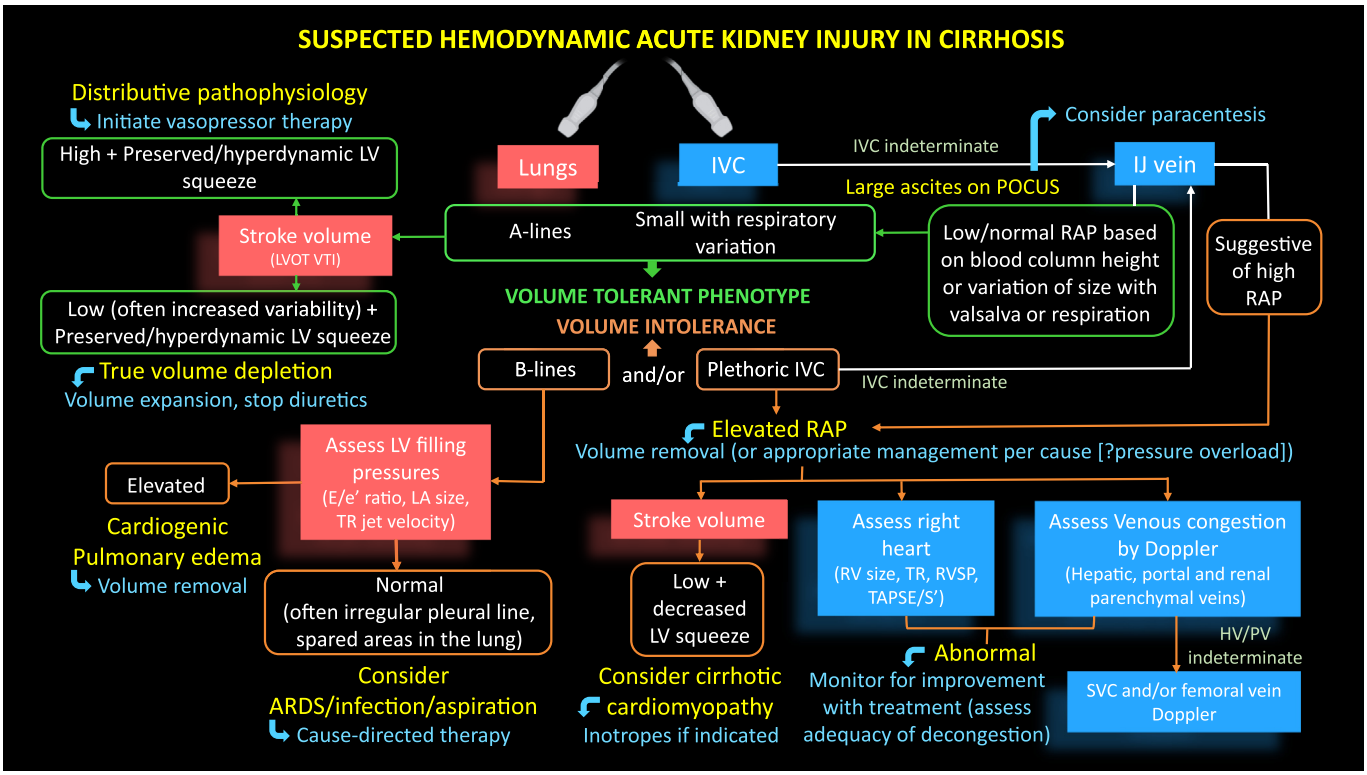

Figure 1. Proposed point-of-care ultrasound (POCUS)-based diagnostic algorithm in a case of cirrhosis and suspected hemodynamic acute kidney injury. The assessment begins with basic sonographic parameters denoting left and right heart pressures, that is, lung and IVC ultrasound, respectively. From there, it advances to parameters assessed by spectral Doppler techniques depending on the focused clinical questions to be answered. Blue boxes indicate right heart, and red boxes denote left heart-related measurements. Green outlines indicate volume tolerance phenotype, and the orange outlines signify volume intolerance. Abbreviations: POCUS, point-of-care ultrasound; IVC, inferior vena cava; IJ, internal jugular; LVOT, left ventricular outflow tract; VTI, velocity time integral; RAP, right atrial pressure; E/e', ratio of the early diastolic waves of the mitral inflow Doppler and mitral annular tissue Doppler; LA, left atrium; TR, tricuspid regurgitation; RV, right ventricle; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; S', tricuspid annular systolic velocity; SVC, superior vena cava; ARDS, acute respiratory distress syndrome; HV, hepatic vein; PV, portal vein. Adopted with permission from Koratala A, Reisinger N. Kidney360. 2022; 3(11):1965-1968. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

CARDIORENAL INTERACTIONS AFTER TIPS

Creating transjugular intrahepatic portosystemic shunt (TIPS) is used to treat portal hypertension and resulting ascites in patients with advanced liver disease and cirrhosis. TIPS reduces the pressure in the portal system, hence lowering the rate of accumulation of fluid in the peritoneal space to allow more efficient lymphatic drainage.

TIPS is associated with immediate changes in hemodynamics due to blood being directed away from the splanchnic vascular bed into the systemic circulation, resulting in an increase in preload and cardiac output and a reduction in systemic vascular resistance and afterload.[26] As such, TIPS may represent an iatrogenic challenge to the heart by exacerbating the already existing hyperkinetic circulation.[27,28] Transient pulmonary hypertension, possibly related to enhanced preload, is a common observation in these patients.[29] With a TIPS, vasodilator substances typically present in the portal circulation are also released into the systemic circulation, leading to further enhancement of vasodilation, which is also driven by increased nitric oxide synthesis secondary to elevated cardiac output and shear stress.[30] The pre-TIPS clinical state would determine to some extent, the potential cardiac consequences of TIPS insertion. While being helpful in replenishing systemic circulation in those patients with arterial hypovolemia, it could paradoxically lead to acute heart failure and pulmonary edema in a subset of patients in whom hypovolemia might not be predominant, in particular those with an impaired right heart function.[31,32] As such, cardiac assessment prior to TIPS placement is helpful to detect heart failure with right-sided congestion in particular and severe pulmonary hypertension, which are considered contraindications for TIPS. Of note, it has been shown that persistence of left ventricular diastolic dysfunction after TIPS portends poor prognosis in this setting as well.[33]

The kidney effects of TIPS have been studied by several investigators. TIPS results in a shift of blood away from portal circulation toward systemic venous system, immediately above the level where the kidney veins drain into the inferior vena cava (IVC). Therefore, it may be thought

to conceivably promote progressive kidney venous congestion and its downstream adverse consequences. Nevertheless, several studies have shown that kidney hemodynamics tend to improve after TIPS placement.[26,34] It is thought that this observation is in part due to increase in cardiac output and consequent amelioration in maladaptive RAAS activation (eg, cardiorenal interactions). As expected, these changes result in an increase in urinary sodium excretion as well as clearance of creatinine.[35,36] The cardiorenal benefits of TIPS can also be explained in part by improvement in endothelial dysfunction that follows mitigation of systemic inflammation through lowering pressure in the portal system and hindering the intestinal translocation of bacteria.

IMPLICATIONS FOR MANAGEMENT OF HRS

Albumin, along with a vasoconstrictor, has been the cornerstone of therapy for HRS. It is thought that the oncotic properties of albumin may help reverse central hypovolemia and its downstream consequences, such as RAAS activation, which are secondary to splanchnic pooling.[37] While the increase in cardiac preload may improve cardiac output, other possibilities such as a direct salutary impact of albumin on cardiac tissue have also been contemplated. In a series of elegant ex vivo animal studies by Bortoluzzi and colleagues, cirrhotic rats that received albumin for volume expansion demonstrated an appropriate response to isoproterenol (a nonselective beta receptor agonist) by increasing their left ventricular contractility, while a similar effect was not observed when the cirrhotic animals received saline or a synthetic colloid (hydroxyethyl starch).[37] Interestingly, the control animals did show similar improvement in cardiac contractility with any of the above-mentioned volume expanders pointing to a characteristic of albumin beyond its ability for volume expansion. When further investigated, the investigators observed that albumin had salutary impact on a variety of mediators that are involved in oxidative stress and inflammation (eg, NF-kb and iNOS) in cardiac issue, which saline and starch lack.[37] As such, in addition to indirect impact on cardiac function through increase in preload, albumin might improve cardiac contractility, leading to enhancement of organ perfusion (eg, increase in glomerular filtration rate) through its direct antioxidant and anti-inflammatory effects on cardiac tissue (that is, cardiorenal interactions). It should be noted, however, that in a recent randomized controlled trial, infusion of 20% human albumin in patients with decompensated cirrhosis and serum albumin level of less than 3 g/dL was not more beneficial than the standard care with regards to new infection, kidney dysfunction, or death.[38] Moreover, in another randomized controlled study to confirm efficacy and safety of terlipressin in subjects with HRS type-1 (the CONFIRM trial), although terlipressin plus albumin was more efficacious in reversal of HRS compared to albumin alone, more cases of respiratory failure were reported in the terlipressin arm.[39] It has been suggested that the higher amounts of albumin used in this trial compared to prior studies may have exceeded the needed dose for intravascular volume repletion, leading to hydrostatic pulmonary edema. Moreover, inhibition of splanchnic vascular pooling by terlipressin and the increase in effective arterial blood volume may have exacerbated this effect.

The increasing recognition of the key role of the heart in the pathophysiology of HRS does have important implications regarding management of HRS. In a prospective study using point-of-care ultrasound/echocardiography, the investigators found that 21% of patients diagnosed with HRS were indeed volume-expanded with IVC diameter of $>$ 2.0 cm and IVC collapsibility index of $<$ 40%.[40] This finding prompted initiation of intravenous diuretics; 30% of the patients experienced reduction of serum creatinine by more than 20% within 48-72 hours. In a more recent study, Pelayo and colleagues used data from right heart catheterization of 127 patients that had been clinically diagnosed with HRS based on current criteria.[41] Surprisingly, a significant subset of these patients was found to have elevated cardiac filling pressures: right atrial pressure $>$ 10 mmHg in 62%, PAWP $>$15 mmHg in 62%, and both right atrial pressure $>$10 mmHg and PAWP $>$15 mmHg in 53%. All patients with high PAWP were switched to diuretic therapy, which, interestingly, was followed by significant improvement in their kidney function.[41] As such, while the group with high filling pressures had a significantly higher serum creatinine on admission (2.0 vs 1.6 mg/dL, $P = 0.016$), their serum creatinine levels on discharge were found to be similar compared to those with normal pressures (1.2 vs 1.0 mg/dL, $P = 0.2$). Improvement of kidney function after diuresis in patients with elevated filling pressures suggests that these patients might actually have hepato-cardiorenal syndrome, which was misdiagnosed as HRS (albeit based on available widely-used criteria) given similar clinical phenotypes. An alternative explanation is that both syndromes coexist, but cardiorenal syndrome is the predominant process in the subset of patients with high cardiac filling pressures (that is, more than half of the cohort). It is of special note that unless an appropriate cardiac workup (eg, in preparation for liver transplant) had taken place, the elevated filling pressures could have remained unnoticed, resulting in the patients not receiving any diuretics because they had been diagnosed with HRS based on clinical criteria.

In general, these observations support cardiorenal physiology as a key driving mechanism for worsening kidney function in a subgroup of patients with cirrhosis who develop HRS, pointing to the heart as the link between the liver and the kidney in this setting.

CONCLUSION

HRS is conventionally regarded as interactions between the liver and the kidney, but other organs such as the heart and lungs may play a more prominent role in the pathophysiology than previously thought. The advances in cardiac studies that have helped diagnose more subtle cardiac abnormalities have revealed that many patients with advanced liver disease and cirrhosis demonstrate these abnormalities. Moreover, accumulating data shows that in many instances, the cardiac dysfunction precedes and

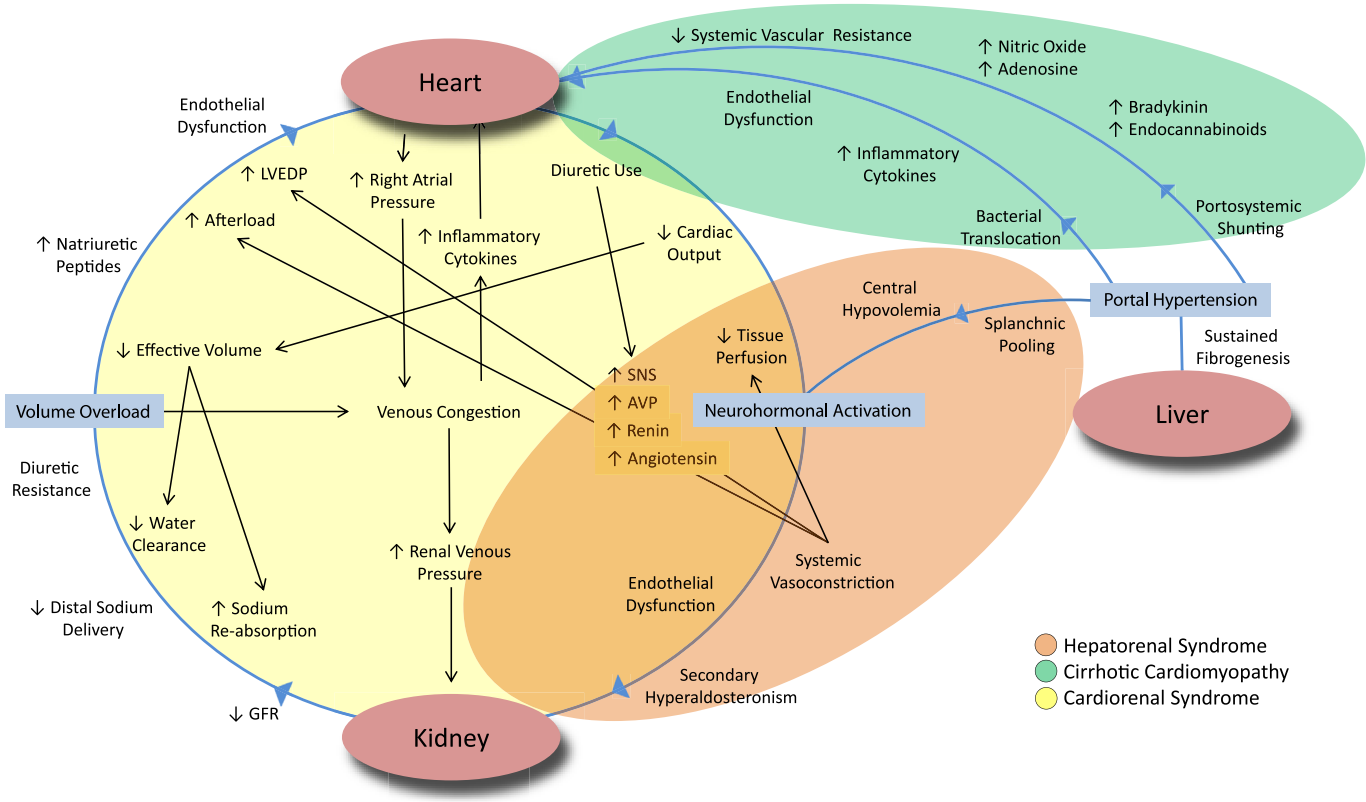

Figure 2. Pathophysiologic pathways linking the liver, heart, and kidney in patients with advanced cirrhosis. The orange circle depicts the conventional concept of hepatorenal syndrome, where kidney dysfunction is mediated through splanchnic vasodilation and consequent neurohormonal activation. The green circle highlights the hepatocardiac pathways through which cirrhosis leads to cardiac dysfunction (that is, cirrhotic cardiomyopathy). The yellow circle summarizes the bidirectional mechanisms linking cardiac dysfunction to aberrant kidney function (that is, cardiorenal syndrome). Abbreviations: SNS, sympathetic nervous system; AVP, arginine vasopressin; GFR, glomerular filtration rate; LVEDP, left ventricular end-diastolic pressure.
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predicts development of kidney disease in such patients. These observations point to the heart as a key player in HRS and challenge the notion that the cardiac abnormalities are either the consequence of aberrancies in hepatorenal interactions or have only minor effects. Moreover, two of the main options for management of HRS (that is, albumin and TIPS) seem to promote their salutary impact on kidney function through their positive effect on cardiac function. Therefore, we propose a more comprehensive view of the pathophysiologic mechanisms of HRS that brings the heart, and its interactions with the kidney, to the forefront of such pathways (Figure 2). This model would help more precisely risk stratify the patients by including an in-depth evaluation of the heart and implementing appropriate management strategies.

AUTHORS' CONTRIBUTIONS

A. Koratala contributed to drafting of article and data collection. F.V. contributed to revising the article critically for important intellectual content. A. Kazory contributed to planning the structure, content, and revising the article critically for important intellectual content.

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